REMARKS

With entry of the instant amendment, claims 1-32, 34, 41, 42, 46, 47, 49, 56, 57, 61, and 62 have been cancelled, claims 33, 35, 39, 48, 50-52, and 54 have been amended, and new claims 63-68 have been added. Claims 38, 40, 43-45, 53, 55, and 58-60 were withdrawn by the Examiner as allegedly not drawn to the elected species. Claims 33, 35-37, 3948, 50-52, 54, and 63-68 are therefore currently under examination.

Cancellation of subject matter is without prejudice for revival for prosecution in a continuation or divisional application.

In order to expedite prosecution, claims 33 and 48 have been amended. The amendments to the claims add no new matter. Claims 33 and 48 have been amended in step (b) to recite a candidate binding molecule that competes for binding with the competitor and binds to the target antigen. This amendment adds no new matter and is supported throughout the application, *e.g.,* at paragraph 40. Claims 33 and 48 have also been amended to reflect that the components of the reactivator system are secreted (*see, e.g.,* the first line of paragraph 97); and that the linkages are covalent linkages (*see, e.g.,* paragraph 20). Further, claims 33 and 48 have been amended to recite that the candidate binding molecule(s) and the competitor(s) are antibodies. Support can be found throughout the application and claims as filed, *e.g.,* at paragraphs 72-74. Last, claims 33 and 48 have been amended to recite a reference antibody and a target antigen. Support can be found, *e.g.,* in claims 32 and 49 as filed.

Claims 35, 39,50-52, and 54 have been amended to correct dependency.

New claims 63 and 66 recite that the host cells are prokaryotic; claims 64 and 67 recite that the host cells are *E. coli*; and claims 65 and 68 recite that the host cells are yeast cells or mammalian cells. Support can be found, *e.g.,* at paragraphs 89, 90, and 97.

Species election requirement

First, with regard to the species election requirement in the Office Communication of October 5, 2005, there was no articulation of that which the Examiner regarded as a species. The restriction simply stated that the species are recited, for example, in

claims 6-12 and 13-15. However, claims are definitions of inventions. Claims are never species (§ MPEP806.04(e)). The MPEP states at § 806.04(f) that "to require restriction between claims limited to species, the claims must not overlap in scope". Applicants note that the "species" recited in claims 43, 44, 45, 58, 59, and 60 overlap in scope with the elected species. Accordingly, the Examiner's withdrawal of these claims as allegedly separate species that do not read on the elected species is improper.

Withdrawn claims 43 and 58 recite that the candidate binding molecules are hybrid antibodies that have at least one CDR in a V_H or V_L that is different from the reference antibody and is from a natural antibody repertoire. Applicants elected the species of candidate binding molecule that is a Fab. A Fab candidate binding molecule has a V_H region and a V_L region. The elected Fab candidate binding molecule need not be naturally occurring. Accordingly, it may have at least one CDR in a V_H and/or V_L that is different from the reference antibody and is from a natural antibody repertoire. The elected Fab species therefore overlaps in scope and reads on the candidate binding molecules of claims 43 and 58. The same holds true for withdrawn claims 44 and 59. Thus, claims 43, 58, 44, and 59 are not properly distinct species.

Similarly, withdrawn claims 45 and 60 relate to a competitor that is a nonhuman antibody and a candidate binding molecule that has at least one human variable region. Again, a Fab candidate binding molecule can have at least one human variable region. Applicants elected species therefore reads on the withdrawn claims. With regard to the competitor, Applicants elected a scFv in response to the species election requirement. An scFv can be a nonhuman antibody. Accordingly, Applicants elected species again overlap in scope with the withdrawn claims.

In view of the foregoing, the Examiner's withdrawal of claims 42, 43, 44, 45, 58, 59, and 60 from examination is not proper. Applicants therefore at a minimum respectfully request that these claims be examined with the elected species.

Rejection under 35 U.S.C. § 112, first paragraph written description

Claims 33-37, 39, 48-52 and 54 were rejected as allegedly not compliant with the written description requirement The Examiner contends that the application discloses only one species and that this constitutes inadequate support for the genus. The Examiner additionally alleges that the claims lack proper support because there is no disclosure of the structures of components of the invention. To the extent that the Examiner believes that the rejection applies to the amended claims, Applicants respectfully traverse.

First, the invention does not concern the discovery of gene function or structure, as in *University of California v. Eli Lilly* 43 USPq2d 1390 (Fed. Cir. 1997), which was cited by the Examiner in support of the rejection. The components employed in the claimed methods are prepared from known components of known function. Applicants have further provided examples of such components. The claims at issue in *Lilly* related to an unknown protein.

Next, the Examiner also cited *University of Rochester v. G.D. Searle & Co.* (cited at page 5 of the Office Action) in support of the allegation that the claims lack written description support. In *Rochester*, the claims at issue related to methods of treating a patient with a compound that inhibited one enzyme, but not another. Unlike the present application, the patentee (the University of Rochester) did not provide examples of such compounds or provide guidance to steer the skilled practitioner toward compounds that could be used to carry out the claimed methods. The University of Rochester also failed to provide evidence that such compounds were otherwise within the knowledge of the practitioner. The courts held that the claims were invalid. The facts here are distinct. Applicants have provided examples of the constituents employed and have steered the practitioner to such components, which are readily available in the art.

Applicants reiterate that it is not the components themselves that are inventive; it is the way they are employed. The function of the written description requirement is to ensure that inventor had possession, as of filing date of application relied upon, of the claimed subject matter. How the specification accomplishes this is not material; it is not necessary that application describe claim limitations exactly, but only so clearly that one having ordinary skill in pertinent art would recognize from disclosure that applicant invented the claimed processes.

The courts have made clear that applicants are not required to describe that which is known. For example, in *In re Herschler,* 200 USPQ 711 (CCPA 1979), the appellant discovered that dimethyl sulfoxide (DMSO) enhances the penetration of a steroidal agent through skin tissue. Physiologically active steroidal agents were known to those of ordinary skill in the art. The priority specification disclosed only one example of such a steroidal agent. The court found that the written description in the priority application was adequate to support broad claims to methods of topically administering a physiologically active steroidal agent by administering the steroidal agent and DMSO. The novelty in that invention was the DMSO solvent, not the steroids.

The facts here are analogous. As noted above, the components of the claimed system are available to those in the art. For example, Applicants provide examples of various responder molecules that can be used, including enzymes that, directly or indirectly, generate a detectable signal using a colored or fluorogenic substrate. Enzymes that confer antibiotic resistance can also be used. Furthermore, non-enzymatic responders can be used such as fluorescent proteins (*see, e.g.,* paragraphs 101-103 of the specification and parent application no. 10/208,730, which is incorporated by reference). Practitioners are further directed (*e.g.,* at paragraphs 20 and 109) to sources such as parent application no. 10/208,730 for additional guidance for inhibitors and reactivators that can be used with various responder molecules. Exemplary inhibitors of enzymatic and fluorescent responder molecules are provided, *e.g.,* in paragraphs 82-86 in parent application no. 10/208,730. Exemplary reactivators of such responder molecules are taught in paragraphs 87-90 of the parent application. Last, in the current claims, the candidate binding molecules, competitor molecules, and reference binding molecules are antibodies (which term includes various fragments of antibodies, as defined in the specification). Nucleic acids encoding such antibodies can readily be obtained by those of skill in the art for use in the invention.

The Examiner further alleges that Applicants have failed to provide information such as the size of the library, size of the genes, and "kind" of genes. The Examiner has provided no support, however, that in view of the advanced level of skill in the art in generating and screening libraries, one of skill would require such information in order to determine that

Applicants were in possession of the invention. Again, the invention is not a new library per se, nor is it a gene of a particularly inventive size, nor is it a "kind" of gene. The inventive aspect of the present invention is the use of the reactivator system components for affinity maturation. Applicants have provided examples and guidance for identifying system components that are readily available in the art and have taught how to construct the components using methods well-known methods in the art.

In view of the foregoing, Applicants have described the invention in terms that satisfy the written description requirement. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 33-37, 39, 48-52, and 54 were rejected for alleged indefiniteness. First, the Examiner contends that claim 33 is indefinite because it lacks an essential step. Although a competitor is used in step (a), the Examiner contends that the claim is indefinite because step (c) does not recite a competitor. The Examiner also alleges that the claim is confusing as to the attachment of the responder inhibitor, referring to Fig. 1 and Fig. 3, which the Examiner describes as showing that the target contains the inhibitor instead of the library of expressing genes. Last, the Examiner alleges that the use of terminologies such as reactivator complex and auto-inhibited responder are not consistent with those in the art and are therefore confusing. Applicants traverse these rejections.

With regard to the rejection of claim 33 as allegedly missing an essential step, in order to expedite prosecution step b has been amended to further state that the responder molecule is activated when a candidate binding molecule competes for binding with the competitor and binds to the target binding ensemble member. The final step is detecting a resulting signal. No essential step is missing, as the detection step does not require reference to the competitor. Applicants therefore respectfully request withdrawal of the rejection.

With regard to the alleged confusion in the attachment of the inhibitor, first, Fig. 1 does not relate to the elected group (*see, e.g.,* the description of Figure 1 at paragraph 14). It does not illustrate a configuration using a responder complex linked to an inhibitor and a binding

molecule, a complex where a responder is linked to an inhibitor and to a binding molecule, and a reactivator complex comprising a binding molecule linked to a reactivator. Further, Fig. 3 illustrates only one potential embodiment of affinity maturation using a reactivation system that is encompassed by the invention (*see, e.g.,* claim 48). This does not render claim 33 indefinite. Claim 33 plainly recites that the auto-inhibited responder complex comprises a responder molecule linked to an inhibitor and linked to a candidate binding molecule.

Last, the Examiner alleges that the terminology employed in the claims is confusing and that terms such as "auto-inhibited responder", "reactivator complex", and the like are not consistent with those in the art. Applicants also traverse this aspect of the rejection. Even assuming *arguendo* that the terminology is inconsistent with the art, Applicants are entitled to be their own lexicographer (*see, e.g.,* the MPEP § 2173.05(a). Applicants have defined the terms (*see, e.g.,* the various terms in the Definitions section beginning on page 7 and the sections beginning on page 26 that further describe responders, reactivators, inhibitors, and competitors). The rejection does not provide any basis for the allegation that one of skill in the art would consider the terms to be inconsistent with the art. The rejection is therefore unfounded.

In view of the foregoing, the claims meet the requirements for being definite. Applicants therefore respectfully request withdrawal of the rejection.

Obviousness type double patenting

Claims 33-37, 39, 48-52, and 54 were provisionally rejected for alleged obviousness type double patenting over claims 1-29 of co-pending application no. 10/208,730. As the Examiner noted, no claims have been allowed. Applicants will gladly consider filing a terminal disclaimer should the conflicting claims be allowed before allowable claims have been identified in the current application.

Rejection under 35 U.S.C. § 102(b)

Claims 33-37, 39, 48-52 and 54 were rejected as allegedly anticipated by Dove *et al.* in U.S. Patent No. 5,925,523 (referred to herein as "Dove"). Dove describes an interaction trap assay. The Examiner alleges that an embodiment in which the bait and prey regulate

expression of a transcriptional repressor (the "first" reporter), which is in turn a transcriptional repressor of a second reporter gene, anticipates the current invention. Applicants respectfully traverse the rejection. As the Examiner knows, in order for a reference to anticipate an invention, it must disclose each and every element that is claimed. Dove fails to do so.

First, the rejection does not articulate which elements of Dove correspond to the elements set forth in the instant claims, thus it is not clear precisely how the Examiner is applying the art to the current claims. The Examiner points to Dove at column 23 , lines 12-63 as allegedly disclosing an auto-inhibited responder complex as claimed. This is the only point in the rejection that discusses an auto-inhibited responder complex. Applicants will therefore focus on this passage.

In claim 33, there are three basic components:

- a competitor;
- a reactivator molecule linked to the target binding ensemble member; and
- a responder molecule linked to an inhibitor and linked to a candidate binding molecule.

In claim 48 there are also three components:

- a competitor;
- a reactivator molecule linked to a candidate binding molecule; and
- a responder molecule linked to an inhibitor and to the target binding ensemble member.

In the current claims, the responder is inhibited (*i.e.*, "auto-inhibited) by the inhibitor to which it is covalently linked. The reactivator displaces the inhibitor from the inhibitor-responder complex to activate the responder. In Dove, at the passages at issue, expression of a reporter molecule is controlled by a repressor. The gene encoding the transcriptional repressor is itself linked to a DNA regulatory sequence. The repressor is expressed when two binding pair members (one of which is attached to an activation domain and one of which is attached to a DNA binding domain that binds noncovalently to the DNA regulatory sequence linked to the repressor gene) bind to one another. When the repressor is

expressed, the reporter molecule is not expressed because the repressor acts to prevent expression. The Examiner thus appears to be alleging that the reporter molecule of Dove would correspond to a responder molecule of the instant invention and that the repressor would correspond to an inhibitor. The Examiner therefore alleges that Dove discloses an auto-inhibited responder complex. Applicants submit, however, that even assuming *arguendo* that the Examiner's interpretation of Dove is accurate, the reference does not anticipate the claims: Dove fails to disclose a reactivator complex.

If a reactivator molecule were to be found in Dove *et al.*, it would need to displace the repressor from the regulatory region governing reporter gene expression, thereby activating expression. Dove teaches no molecule that serves this function and moreover, that is part of a reactivator complex as set forth in the claims. For example, in Dove a candidate molecule may be tested for the ability to disrupt binding between the binding pair members, thereby preventing expression of the repressor. Is the Examiner proposing that such a candidate binding molecule (*i.e.*, that disrupts binding of the binding pair members) may serve as the reactivator because it would "displace" the repressor that prevents expression of the reporter? Even if one were to adopt this interpretation, such a proposed reactivator does not comport with the reactivator complex as specified in the claims. In claim 33, the reactivator is linked to a target binding ensemble member. However, a candidate binding molecule in Dove is not linked to a target binding ensemble member. In claim 48, the reactivator is linked to a candidate binding molecule. Dove does not teach a candidate binding molecule linked to itself. Thus, a candidate binding molecule in Dove does not serve as a reactivator in applicants' invention. If the candidate binding molecule in Dove is not a reactivator, then which other molecule is? The passages cited by the Examiner in fact fail to identify such a reactivator molecule.

Dove additionally fails to disclose a system that is used for affinity maturation. In particular Dove fails to disclose that candidate binding molecules are selected that have a greater affinity for the target binding ensemble member in than a reference binding molecule.

Further, with regard to the amended claims, Dove does not teach a system in which the components are secreted. In Dove, the interaction trap assay works within the cell, *i.e.*, the trap assay involves transcriptional regulatory domains that activate gene expression.

Although Dove asserts that antibodies can be identified using this method, there is no teaching of how functional antibodies can be expressed successfully in the reducing environment of the cytosol.

Thus, the cited reference fails on many counts to teach each and every element of the claimed invention. Accordingly, Dove does not anticipate the current claims. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 103

Claims 33-37, 39, 48-52 and 54 were also rejected as allegedly obvious in view of Balint (WO/00/71702) in view of Strynadka *et al.*, or Yanagawa *et al.* (2005/0142623). The Examiner characterizes Balint as teaching fragment complementation in which two complementing fragments of an enzyme are each linked to a binding pair member. When the binding pairs bind, enzymatic activity is reconstituted. The Examiner further describes Balint as teaching that such a system can be used to screen for inhibitors of the interaction of the two binding pairs where the presence of the inhibitor results in inhibition of enzyme activity. The Eaminer then describes Strynadka (or Yanagawa, referring to Strynadka) as teaching a β-lactamase inhibitor protein (BLIP). The Examiner alleges that it would have been obvious that BLIP could have been used in the methods of Balint (or Dove) and that one of skill would have been motivated to do so because of the advantages (which were not described in the rejection) in doing so. Applicants respectfully traverse the rejection.

According to M.P.E.P. § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all the claim limitations. The rejection does not meet these requirements. First, the references do not teach or suggest all of the elements of the claims. The invention is not merely the use of BLIP in an affinity maturation protocol. There are additional elements in the claims. At a minimum, the cited art does not teach or suggest a responder complex as set forth in claims 33 and 48 in which

the responder molecule is linked an inhibitor and to a candidate binding molecule (claim 33) or a target binding ensemble member (claim 48). Furthermore, the cited art additionally fails to teach or suggest a reactivator complex. Last, the cited art does not teach or suggest each step of the claimed methods. Accordingly, the cited art fails to teach or suggest all of the elements present in the claims.

Applicants further note that the rejection fails to provide a proper motivation for combining or modifying the teachings in the cited art. The rejection does not establish that the ability of BLIP to adapt to a variety of β-lactamases would lead one of skill in the art to the claimed invention.

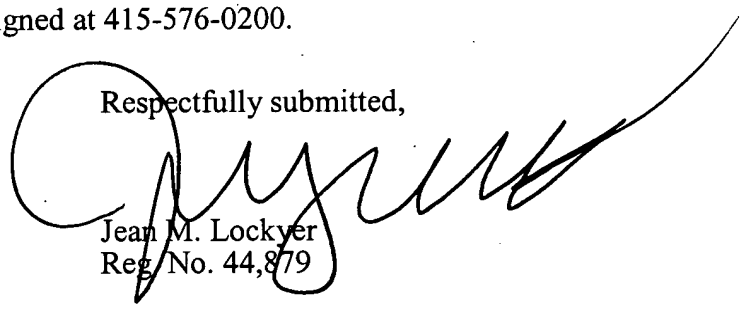
In view of the foregoing, the Examiner has failed to establish a proper case of obviousness. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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